

DETAILED ACTION

Claim Status and Formal Matters

This action is in response to papers filed 3/11/2010.

Claims 2, 4-5, 9, 13, 16-19, 23, 28-30, 32-35 are pending.

Claims 16-19, 23, 28-30, 32-35 have been withdrawn.

The 102 of Ahr has been withdrawn as Ahr does not teach the claimed probes.

Priority

The instant application was filed 5/1/2006 and is a national stage entry of PCT/GB03/05102 filed 11/21/2003 and claims priority to United Kingdom Patent Application 0227238.3 filed on 11/21/2002.

Specification-New Grounds

1. The amendment filed 3/11/2010, 10/3/2008 and 7/6/2009 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. MPEP 2163.07 II states:

An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of the error in the specification, but also recognize the appropriate correction. In re Odd, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971).

The added material which is not supported by the original disclosure is as follows:

The specification and sequence listing have been amended numerous times to make the sequence listing consistent with the SEQ ID NO. The instant response further amends SEQ ID NO 36 to indicate it is 527 nucleotides.

The instant response has provided a sequence alignment in an attempt to demonstrate that non new matter has been added by previous amendments. However a partial examination of the alignments provided has demonstrated New Matter has been added.

SEQ ID 313 is indicated as being 554 nucleotides; however page 24 of the alignment demonstrates it only has 170 nucleotide identities to SEQ ID NO 15 of the instant specification.

SEQ ID 403 is indicated as being 202 nucleotides; however page 112 of the alignment demonstrates it only has 200 nucleotide identities to SEQ ID NO 66 of the instant specification.

SEQ ID 406 is indicated as being 644 nucleotides; however page 115 of the alignment demonstrates it only has 641 nucleotide identities to SEQ ID NO 68 of the instant specification.

SEQ ID 469 is indicated as being 161 nucleotides; however page 197 of the alignment demonstrates it only has 159 nucleotide identities to SEQ ID NO 116 of the instant specification.

SEQ ID 471 is indicated as being 28 nucleotides; however page 198 of the alignment demonstrates it only has 8 nucleotide identities to SEQ ID NO 117 of the instant specification.

SEQ ID 483 is indicated as being 519 nucleotides; however page 213 of the alignment demonstrates it only has 516 nucleotide identities to SEQ ID NO 128 of the instant specification.

SEQ ID 518 is indicated as being 502 nucleotides; however page 255 of the alignment demonstrates it only has 499 nucleotide identities to SEQ ID NO 155 of the instant specification.

SEQ ID 631 is indicated as being 493 nucleotides; however page 377 of the alignment demonstrates it only has 491 nucleotide identities to SEQ ID NO 232 of the instant specification.

SEQ ID 661 is indicated as being 256 nucleotides; however page 425 of the alignment demonstrates it only has 253 nucleotide identities to SEQ ID NO 260 of the instant specification.

SEQ ID 673 is indicated as being 683 nucleotides; however page 435 of the alignment demonstrates it only has 127 nucleotide identities to SEQ ID NO 268 of the instant specification.

SEQ ID 679 is indicated as being 688 nucleotides; however page 440 of the alignment demonstrates it only has 682 nucleotide identities to SEQ ID NO 272 of the instant specification.

SEQ ID 686 is indicated as being 603 nucleotides; however page 447 of the alignment demonstrates it only has 28 nucleotide identities to SEQ ID NO 277 of the instant specification.

SEQ ID 702 is indicated as being 709 nucleotides; however page 470 of the alignment demonstrates it only has 705 nucleotide identities to SEQ ID NO 292 of the instant specification.

SEQ ID 719 is indicated as being 492 nucleotides; however page 496 of the alignment demonstrates it only has 489 nucleotide identities to SEQ ID NO 306 of the instant specification.

SEQ ID 722 is indicated as being 327 nucleotides; however page 502 of the alignment demonstrates it only has 325 nucleotide identities to SEQ ID NO 309 of the instant specification.

SEQ ID 310 is indicated as being 273 nucleotides; however page 503 of the alignment demonstrates it only has 272 nucleotide identities to SEQ ID NO 310 of the instant specification.

SEQ ID 825 is indicated as being 741 nucleotides; however page 542 of the alignment demonstrates it only has 735 nucleotide identities to SEQ ID NO 332 of the instant specification.

SEQ ID 898 is indicated as being 511 nucleotides; however page 594 of the alignment demonstrates it only has 509 nucleotide identities to SEQ ID NO 360 of the instant specification.

SEQ ID 899 is indicated as being 16 nucleotides; however page 596 of the alignment demonstrates it only has 12 nucleotide identities to SEQ ID NO 361 of the instant specification.

SEQ ID 904 is indicated as being 649 nucleotides; however page 600 of the alignment demonstrates it only has 648 nucleotide identities to SEQ ID NO 364 of the instant specification.

SEQ ID 917 is indicated as being 483 nucleotides; however page 620 of the alignment demonstrates it only has 481 nucleotide identities to SEQ ID NO 375 of the instant specification.

SEQ ID 947 is indicated as being 646 nucleotides; however page 628 of the alignment demonstrates it only has 641 nucleotide identities to SEQ ID NO 379 of the instant specification.

SEQ ID 1071 is indicated as being 571 nucleotides; however page 634 of the alignment demonstrates it only has 569 nucleotide identities to SEQ ID NO 383 of the instant specification.

SEQ ID 1109 is indicated as being 601 nucleotides; however page 644 of the alignment demonstrates it only has 594 nucleotide identities to SEQ ID NO 389 of the instant specification.

SEQ ID 1125 is indicated as being 407 nucleotides; however page 648 of the alignment demonstrates it only has 404 nucleotide identities to SEQ ID NO 391 of the instant specification.

SEQ ID 1193 is indicated as being 900 nucleotides; however page 682 of the alignment demonstrates it only has 896 nucleotide identities to SEQ ID NO 409 of the instant specification.

SEQ ID 1204 is indicated as being 365 nucleotides; however page 699 of the alignment demonstrates it only has 213 nucleotide identities to SEQ ID NO 419 of the instant specification.

SEQ ID 1205 is indicated as being 299 nucleotides; however page 700 of the alignment demonstrates it only has 241 nucleotide identities to SEQ ID NO 420 of the instant specification.

SEQ ID 1210 is indicated as being 702 nucleotides; however page 707 of the alignment demonstrates it only has 68 nucleotide identities to SEQ ID NO 424 of the instant specification.

SEQ ID 1220 is indicated as being 1354 nucleotides; however page 725 of the alignment demonstrates it only has 1343 nucleotide identity to SEQ ID NO 434 of the instant specification.

SEQ ID 1255 is indicated as being 928 nucleotides; however page 740 of the alignment demonstrates it only has 68 nucleotide identities to SEQ ID NO 442 of the instant specification.

Thus the nucleic acid sequence alignment provided by applicant in the instant response demonstrate numerous differences are present between the previous sequence listings and the instant sequence listing and thus the instant sequence listing introduces new matter.

Response to Arguments

The response traverses the New Matter Objection. The examiner has modified the instant rejection in view of the amendments to the specification and response. Thus

the specific issues with discrepancies between the lengths in the table and the sequence listing have been withdrawn. However, the alignment of sequences provided with the instant response has demonstrated (as partially reviewed above) that the sequence listing at time of filing is different than the sequences of the instant disclosure and thus introduces new matter contrary to the assertion of the response.

The response continues by asserting the discrepancies between the sequences are minor and would have been recognized by one of skill in the art. These arguments have been thoroughly reviewed but are not considered persuasive as the alignment demonstrates SEQ ID 313 is indicated as being 554 nucleotides; however page 24 of the alignment demonstrates it only has 170 nucleotide identities to SEQ ID NO 15 of the instant specification. The examiner contends a 374 nucleotide difference is not a minor discrepancy or an obvious error, but New Matter.

The examiner has withdrawn the arguments to the removed clones, in view of the amendment and the response.

Thus as the sequence alignment demonstrate new matter has been added to the specification the objection is maintained.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 2, 4-5, 9 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is drawn to the use of the claimed 351 oligonucleotide probes.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in *re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

Amended claim 2 is drawn to a set of oligonucleotide probes consisting of not more than 1000 oligonucleotides and said set comprising the 351 oligonucleotides having the sequences set forth in the recited SEQ ID NO, with the proviso that at least one of said 351 oligonucleotides may be replaced with either (i) an oligonucleotide

fragment of the one of said 351 oligonucleotides being replaced, which fragment is at least 30 nucleotides in length; (ii) an oligonucleotide having a sequence entirely complementary to the one of said 351 oligonucleotide being replaced, or to a fragment thereof which is at least 30 nucleotides in length or (iii) an oligonucleotide having at least 80% identity to the one of said 351 oligonucleotide being replaced or to a fragment thereof which is at least 30 nucleotides in length.

For the specification to be enabling for the set of oligonucleotide probes claimed, it must teach how to use the probe set for diagnosis of disease.

The amount of direction or guidance and the Presence and absence of working examples.

The specification, "different sets of probes may be used in techniques to prepare gene expression patterns and identify, diagnose or monitor different states, such as diseases, conditions or stages thereof" (see page 1, 1st paragraph).

The specification teaches, "we now describe probes and sets of probes derived from cells which are not disease cells and which have not contacted disease cells, which correspond to genes which exhibit altered expression in normal versus disease individuals, for use in methods of identifying, diagnosing or monitoring certain conditions, particularly diseases or stages thereof" (see last paragraph page 4 to top of page 5).

Example 1 of the specification teaches on page 64 that 497 genes were eliminated and 938 genes remained that were normalized to different external controls (page 65). The specification teaches that correct prediction was obtained in most

breast cancer cell lines (page 65). The specification teaches on page 65 that this model correctly identified 41 of 46 non cancer samples (page 65). Thus example 1 of the instant specification suggests that 938 genes can be used to identify breast cancer. It is noted that the specification does not specifically recite with respect to example 1 which 938 probes were informative. Further is noted that Table 6 asserts that from 23 to 139 probes were used as diagnostic, but states an error rate of between 13 and 20%.

Example 2 of the specification teaches that an array of 758 cDNA clones were used instead of the 1435 probes in example 1 (page 67). The specification does not teach the number of the 758 cDNA clones required to be predictive, but notes in table 7 that none of the 14 subjects analyzed were predicted to have Alzheimer's by the method.

Example 3 of the specification a classification model that is generated by using 719 cDNA (page 71). The specification teaches that 111 of the 719 cDNA are described in Table 2 (page 71).

Example 3 of the specification teaches that 730 cDNA clones were picked and 520 probes were sequenced (page 73).

The specification does not provide examples of replacing any SEQ ID NO 117 which is only 28 nucleotides. The specification teaches SEQ ID NO 138 which is 4 nucleotides. The specification teaches SEQ ID NO 225 which is only 17 nucleotides . The specification teaches SEQ ID NO 361 which is only 12 nucleotides. It would thus be unpredictable to replace sequence of less than 30 nucleotides with sequences of at least 30 nucleotides without specific guidance.

Further SEQ ID NO 346 has a stretch of 46 adenines. SEQ ID NO 335 has a stretch of 33 adenines. SEQ ID NO 429 has a stretch of 33 adenines. Thus replacement of the full length claimed nucleic acid sequences with a fragment of the poly adenine would allow for detection of any nucleic acid sequence with a poly T, such as every reverse transcribed RNA, but not the specific sequences of this SEQ ID NO. Thus the use of any fragment of at least 30 nucleotides is unpredictable.

The state of prior art and the predictability or unpredictability of the art:

The art of Cheung et al (Nature Genetics, 2003, volume 33, pages 422-425) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3).

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art of Wu (Journal of Pathology, 2001, volume 195, pages 53-65). Wu teaches that gene expression data must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that

can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The prior art of Newton et al (Journal of Computational Biology, 2001, volume 8, pages 37-52) further teaches the difficulty in applying gene expression results. Newton et al teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph).

Draghici et al (Trends in Genetics (2006) volume 22, pages 101-109) that shortening probes from 30 nucleotides to 25 nucleotides reduces the sensitivity 10 fold (page 103, 1st column, 1st full paragraph). Draghici teaches that splice variant introduce variation in microarrays as short probes to not correctly identify the expression of all splice variants, while long probes will detect all variants (page 107, 2nd Column, 2nd paragraph). Draghici teaches that a limited amount of complementarity can be sufficient to enable binding of two unrelated sequences (page 107, 2nd column, last paragraph).

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed, one would first have to determine if one of skill in the art could make and predictably use the invention as claimed. Thus the

artisan would have to determine if the claimed collection of oligonucleotides would allow detection or diagnosis of breast cancer or Alzheimer's as asserted in the specification.

It would be unpredictable in that the artisan would first have to determine which nucleic acids are informative in the instant method. This would be unpredictable in view of the New Matter objection. The New Matter objection demonstrates that the sequences of the initial disclosure are different than those of the instant specification. Thus the artisan could not predictably determine which nucleic acid is required and allows for diagnosis. It would thus be unpredictable to use a collection of probes for detection or diagnosis of a disease without knowledge of which probes are truly informative and certainly the probes claimed are actually those viewed as informative.

It would be unpredictable to use a probe that is only 30 nucleotides in length and at least 80% identical to the claimed sequences as SEQ ID NO 346 has a stretch of 46 adenines. SEQ ID NO 335 has a stretch of 33 adenines. SEQ ID NO 429 has a stretch of 33 adenines. Thus replacement of the full length claimed nucleic acid sequences with a fragment of the poly Adenine sequences would not allow detection of the full length message. Thus as the sequence claimed contain fragments of 30 nucleotides with 80% identity that would hybridize every polyT tails it would be unpredictable to practice the invention as claimed. Further in view of the teachings of Draghici it would be unpredictable to use shorter probes to detect longer sequences without specific guidance that the claimed probes would specifically hybridize to only sequence complementary to the full SEQ ID NO and thus identify the nucleotide sequence that allows for diagnosis.

It would be further unpredictable to replace nucleic acid sequences of less than 30 nucleotides with sequences of at least 30 nucleotides. The specification does not provide examples of replacing any SEQ ID NO 117 which is only 28 nucleotides. The specification teaches SEQ ID NO 138 which is 4 nucleotides. The specification teaches SEQ ID NO 225 which is only 17 nucleotides. The specification teaches SEQ ID NO 361 which is only 12 nucleotides. It would thus be unpredictable to replace sequence of less than 30 nucleotides with sequences of at least 30 nucleotides without specific guidance.

This would be replete with unpredictable trial and error analysis because the specification does not how the expressed probe set is used to diagnose disease. Specifically the specification has in tables 1a, 1b, 2a, 2 b, 4 and 9 of the specification identify sequences that are informative of a disease state, breast cancer, Alzheimer's or Alzheimer's and breast cancer, however the specification does not teach how the combination of SEQ ID NO diagnose Alzheimer's or breast cancer. Thus the skilled artisan would have to determine if all the claimed capture probes or a specific subcombination of probes would have to demonstrate an increase or decrease expression to result in the diagnosis of any disease or Alzheimer's or breast cancer. This would be further unpredictable as the various tables do not recite that the claimed genes are informative.

Response to Arguments

The response correctly identifies that part of the unpredictability indicated by the examiner is due to the discrepancies in the sequence listing and New Matter issues

raised above. The examiner notes that the alignment provided by applicant further demonstrates that one of skill in the art could not make and use the claimed invention predictably due to the numerous discrepancies outlined in the New Matter objection above, as several of these discrepancies are in claimed SEQ ID NO, including SEQ ID NO 11, 25, 36, 66, 68, 116, 117, 128, 155, 182, 232, 260, 268, 272, 309, 310, 332, 361, 364, 375, 383, 389, 409, 419, 420, 424 and 434. (The examiner notes this is a partial analysis, which demonstrates the differences in sequences).

The response correctly identifies the other enablement issue is the length of probe required to replace the full length probe in parts i, ii, or iii of claim 1. The response asserts the amendment to require at least 30 nucleotides has overcome this issue. This argument has been thoroughly reviewed but is not considered persuasive as the claims require SEQ ID NO 335, 346, and 429 which contain long poly adenine tracts and would hybridize to poly T tails of reverse transcribed poly A tails or the complement to the long poly adenine tracts would directly hybridize to poly A tails.

Further, it would be unpredictable to replace claimed SEQ ID NO 117, 138, 226, and 361 with nucleic acid fragments of at least 30 nucleotides, when the sequences are less than 30 nucleotides without specific guidance from the specification or prior art.

Thus in view of discrepancies in the sequence listing and New Matter objection the artisan would not be enabled to make the claimed invention as the sequences required. Further, it would be unpredictable to use any 30 nucleotide fragment as several of these would not be specific as they would hybridize to the poly-A sequences in the sequences. Finally it would be unpredictable to replace sequences of less than

30 nucleotides with sequences of greater than 30 nucleotides without specific guidance on what nucleotides to add.

Summary

No claims are allowed.

Conclusion

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **STEVEN C. POHNERT** whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Steven C Pohnert/
Primary Examiner, Art Unit 1634